VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

#225

GUIDANCE FOR INDUSTRY

Electronic Exchange of Documents: File Format Recommendations

VICH GL53

Draft Guidance

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments on the guidance to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
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VICH GL53 (EFF) - ELECTRONIC FILE FORMAT
For consultation at Step 4

ELECTRONIC EXCHANGE OF DOCUMENTS: FILE FORMAT RECOMMENDATIONS

Recommended for Consultation
at Step 4 of the VICH Process
by the VICH Steering Committee

This draft guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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Guidance for Industry
Electronic Exchange of Documents: File Format Recommendations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1 Introduction

1.1 Objective

The electronic exchange of regulatory documents concerning veterinary medicinal products between industry and agencies is commonplace. Global harmonization of the technical recommendations for the electronic file format of documents is seen as a fundamental starting point to realizing the potential benefits.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

1.2 Scope

The scope of this draft guidance is to recommend electronic file format specifications for individual documents and collections of multiple related documents that need no subsequent editing and are utilized for electronic exchange between industry and regulators in the context of regulatory approval of veterinary medicinal products. It applies to communication or data exchanged as documents in the context of all regulatory procedures where regulators accept electronic transfer of such documents. This may include but is not limited to applications for initial marketing authorizations, related pre-submission or post-authorization procedures, applications for maximum residue limits, clinical trial applications, drug / active substance master files or requests for regulatory or scientific advice.

Working documents that need to be maintained in their native file format for further editing (e.g. Microsoft (MS) Word), such as proposed label texts, are out of the scope of this draft guidance.

Where electronic exchange of documents in the scope of this draft guidance is already accepted by regulators at the time of adoption of this document, the actual time of application of this draft guidance is recommended within one year after adoption but it may be voluntarily applied earlier.

For business processes that are still paper-based, implementation of this guidance may be suspended by regulators until electronic exchange can be accepted.

Specific recommendations may apply to region-specific documents, for example, application forms or facsimile copies of labels for use in the region.

The draft guidance is addressed as a draft guidance document to industry; however, voluntary acceptance of the principles of this draft guidance for documents created by regulatory authorities for exchange with industry is also encouraged.

1.3 General Recommendations

It is recommended that a standard interchange file format for documents that do not need to be modified or extracted into databases:

- can be generated from other electronic source formats or digitized from paper;
- is designed for viewing and/or printing;
- allows the use of a viewer whose specifications are in the public domain;
- relies on major international standards like the International Organization for Standardization (ISO);
- is both device and resolution independent;
- retains the content and the layout of the original document;
- remains useable and accessible long-term;
- preserves the visual appearance of file content over time;
- supports regulatory review needs, including searchable text;
- builds on a format that already has broad acceptance among industry and regulators;
- is a cost-efficient solution for the veterinary sector.

2 Portable Document Format (PDF) File Format Recommendations

2.1 Single-file transfer

Option 1: PDF/A-conforming files:

A standard interchange format for electronic transfer of documents that meets the above needs is PDF/A, which restricts PDF in a way that it is optimized for exchange and long-term reproducibility of the content.

PDF files that conform to [ISO-19005-1:2005], [ISO-19005-2:2011] or [ISO-19005-3:2012] are accepted for all types of electronic exchange of non-editable documents between industry and regulatory agencies. Note however that the use of embedded files or PDF portfolios / PDF packages, though it may conform to PDF/A recommendations, does not meet VICH review recommendations (see table below and section 2.3 for further details).

Minimum PDF/A conformance level, i.e. Level B conformance (PDF/A-1b, PDF/A-2b or PDF/A-3b) is recommended. Compliance with higher levels of PDF/A conformance such as Level A is not critical but such files will be accepted as well.

The specification is available from the ISO web site: http://www.iso.org/.

It is important to note that also the application (PDF reader), that is reading and processing PDF files complying with a specified conformance level, should comply with all relevant recommendations as specified in [ISO-19005] to ensure that the document is correctly displayed or printed.

Note that the PDF/A specification alone cannot ensure that the visual appearance of the content accurately reflects the original source material used to create the conforming file.

Applicants therefore should control the process used to create a conforming file to assure that a PDF/A file is an accurate visual representation of the original source document. Potential issues to be observed are incorrect or missing characters caused by inappropriate font substitution, or a negative impact on quality of images due to inappropriate downsampling or poor compression. Applicants should also be aware that the quality of elements like graphics is already determined within the authoring software (e.g. the word processing software used).

Option 2: Minimum recommendations for non-PDF/A conforming files:

Where a document does not conform to PDF/A recommendations, applicants should observe the following minimum recommendations. These recommendations should be followed to meet VICH review needs, to increase long-term sustainability and to ease a potential conversion process to an archive format (i.e. PDF/A) and therefore also make reference to some important PDF/A recommendations.

Criterion	Recommendation	Comment
PDF Version	Files have been created and saved as PDF 1.4, 1.5, 1.6, or PDF 1.7.	Based on [ISO 32000-1:2008] Document management -- Portable document format -- Part 1: PDF 1.7. Use of PDF Extension Levels to version 1.7 does not lead to rejection / invalidation of files.
Security settings	No type of security on individual files.	Password protection preventing access to the document or restricting permissions, e.g. to prevent printing or the copying of text, is not allowed. Documents which may not be able to be stripped of all security settings are exempted. This includes references taken from journals and other publications or PDF forms provided by regulatory agencies. To provide a secure mechanism for exchange of confidential information between applicants and regulatory agencies the use of appropriate tools like secure web portals or secure gateway-to-gateway communication is recommended. PDF files in such cases should not be password-protected for reasons of security. Password-protected, encrypted ZIP or PDF files should be used only in case of unprotected transfer (e.g. via email) and if agreed between applicant and receiving agency. Note that encrypted PDF files cannot be converted to PDF/A. Please consult guidance of national/regional authorities concerning available methods for file transfer.

Criterion	Recommendation	Comment
Prohibited PDF features	PDF files should not contain:	
	• JavaScript and executable file launches	Region-specific documents like electronic application forms with JavaScript functionality provided by regulatory agencies are exempted.
	• External content references (Everything needed to render or print a PDF file must be contained within the file.)	Note that external hyperlinks to other PDF documents if used in a multi-file submission (see section 2.2) or to web pages are in conformance with PDF/A recommendations.
	• Dynamic content which can include audio, video, 3D content or other special effects and animations	
	• Attachments (embedded files)	Embedded files do not meet the VICH review needs as they can be easily overlooked during compilation / review of documents and may complicate technical validation.

Criterion	Recommendation	Comment
Font embedding	Every font used for visible text should be embedded within the PDF file.	PDF/A recommends embedding of fonts used for rendition of visible text only. Thus invisible fonts used in scanned documents for creating searchable text by an Optical Character Recognition (OCR) routine may be embedded but are exempted from an embedding recommendation. PDF/A recommends only embedding of the subset of characters actually used in a given font. Embedding complete fonts needlessly increases the size of the PDF file. All embedded fonts must also be legally embeddable, i.e. license agreements must allow unlimited embedding into the PDF file, either fully or as a subset, for the purpose of printing or viewing the document. Subsetting and use of commonly used fonts is recommended from a copyright perspective.
File integrity	Files must not be corrupted.	For technical validation a check may be achieved by opening a file in a PDF reader which is compliant to [ISO 32000-1:2008]. If the file opens without error, the PDF file is considered to be conformant. Note that this method may not detect all possible errors within a file. To avoid delays in the review process the applicant should carefully check file integrity before transfer. Browsing the complete document page by page will assure that the full content is accessible. In combination with above technical PDF check by regulators, this simple manual check effectively assures that a reviewer can fully access all received documents.

2.2 Multiple-file transfer

In case of transfers of multiple documents some regulatory agencies recommend or even request the use of inter-document hyperlinks to other PDF files to improve navigation efficiency through such submissions. Note that inter-document hyperlinks may become non-functional when files are maintained within an agency's document management system. In the latter case they will be useless for navigation and therefore may not be recommended. Applicants should consult relevant guidance of national/regional authorities.

Note that external hyperlinks to other documents in a submission in principle are in conformance with PDF/A recommendations. Where PDF/A is used, authors however should observe that specific hyperlink actions are forbidden in [ISO-19005] (see section 2.3 for further details), and reviewers may need to configure ISO compliant readers to make external hyperlinks actionable.

When such inter-document hyperlinks are requested, additionally to section 2.1, the following recommendations apply:

Criterion	Recommendation	Comment
Inter-document hyperlinks or bookmarks	Destination file path	Inter-document hyperlinks or bookmarks should refer to other PDF files by using relative file paths. To maintain the functionality of hyperlinks, all files should remain in the same relative location in a folder structure after hyperlinking. To allow reading on certain devices, using non-Windows operating systems, hyperlinks and bookmarks should be configured as specified in [ISO 32000-1:2008]. Specifically the paths should use forward slashes. Consult the PDF specifications as in [ISO 32000-1:2008], section 7.11.2.3 for further detail. Please note, that some PDF tools display the path for the link with backslashes, though the link in the PDF file is fully conforming to these ISO specifications. Open the file with a simple text editor or validate with an appropriate tool to confirm conformance in case of doubt.

2.3 Best-practice recommendations

There are additional factors that are considered good practice for preparation of regulatory relevant documents. PDF files that are not in conformance with such practice will not be rejected by regulatory agencies however applicants are reminded that following these best practices will significantly enhance the efficiency of any review process.

Factor	Recommendation
File size	File size of a single file should be limited to 100 MB.
Fonts	It is recommended to use fonts that are used by most text processors like Arial, Courier and Times New Roman or other fonts with similar level of usage. No customized fonts should be used. Use an adequate font size that ensures legibility. Use black font color for normal text (blue font may be used for hypertext links.) For languages not based on Latin Characters like Japanese an appropriate multi-byte character font supporting Unicode should be used.

Factor	Recommendation
Graphics / Images	When creating PDF files containing graphics or images, use lossless compression until the final rendition is created. Alternatively use the most limited / highest-quality lossy compression that does not compromise visual quality. For files containing color images / color photos consider a color model based on RGB. As sRGB (standard RGB color space as specified in [International Electrotechnical Commission (IEC) 61966-2-1]) is the native color space for usual source applications, operating systems and most digital cameras and scanners, this avoids conversion to another color model and potential negative impact on image fidelity.
Hyperlinks + bookmarks (general recommendations)	Intra-document hyperlinks and bookmarks should be used to assist the reviewers in navigating through the content of a submitted document. Where recommended by regulatory agencies, inter-document hyperlinks and bookmarks should be used to assist the reviewers in navigating through the content of a multi-file submission. Text hyperlinks should be visibly distinct from other text (e.g. blue text may be used). When creating bookmarks and hyperlinks, the magnification setting should be set to "Inherit Zoom". Where bookmarks are used the initial view of the PDF file should be set as "Bookmarks Panel and Page". Hyperlinks to web pages are also appropriate if they are active and the destination is given as a valid web address, also known as uniform resource locator (URL). All URL's should be displayed as a fully qualified URL such as: http://www.vichsec.org/. As URLs may change after preparation of a document, hyperlinks to web pages should however not be used for any content relevant for the assessment of the transferred file(s). In such cases a PDF rendition of the page(s) should be created and submitted as a separate document.

Factor	Recommendation
Hyperlinks from PDF to PDF files	When setting hyperlinks between PDF documents, in the PDF writer the link action to jump to a page view of another ("remote") PDF file should be chosen. Technically this is known as a "Remote Go-To Action". An action to open another file should not be chosen. Technical background: Because JavaScript and executable file launches are forbidden in [ISO-19005], a hyperlink cannot be made by such means. Such hyperlinks may also be lost during PDF/A creation. Instead, hyperlinks should be provided as specified in [ISO 32000-1:2008], section 12.6.4.3 "Remote Go-To Actions" (GoToR). In case of doubt, use of correct hyperlinks parameters can be confirmed with the help of a simple text editor.
Hyperlinks to other destination file formats	In exceptional cases, hyperlinks to open a file of a different file format may be provided (e.g. to graphic files as specified in section 3 or to an MS Word file). When setting hyperlinks to non-PDF documents, in the PDF writer the link action to open a web page should be chosen to enter the Uniform Resource Identifier (URI) of the destination file, i.e. the full name and where applicable the destination file path. Technically this is known as an "URI Action". Note that recommendations of section 2.2 for file paths apply. Technical background: Note that hyperlinks based on a "Launch Action" (see [ISO 32000-1:2008], section 12.6.4.5) are not allowed in [ISO-19005]. Such hyperlinks may also be lost during PDF/A creation. Therefore hyperlinks to other file formats should use the URI action as specified in [ISO 32000-1:2008], section 12.6.4.7 "URI Actions".
Page numbering	Pages within an individual file should be numbered. The initial page of the source document and PDF document should be numbered page 1.
Page orientation	Pages should be properly oriented. For example, you should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation.
Page view settings	Use "default" initial page view settings for page layout and magnification.
PDF portfolio / PDF package (portable collections)	The use of PDF portfolios is in conformance with PDF/A recommendations. Nevertheless use of such PDF collections should be avoided as its functionality may rely on presence of other software and thus may cause issues during the review process.

Factor	Recommendation
Print area	Print area for pages should fit on ISO 216:2007 A4 (210 x 297 mm) and a Letter format (8.5 inches by 11 inches) sheet of paper ensuring sufficient margins and readability. Files used for local/regional submission only (including mock-ups) are exempted.
Resolution of scanned elements	If scanning is unavoidable the following scanning parameters should be used: Scanning of text documents at a resolution of not less than 300 dots per inch (dpi) will normally balance legibility and file size. Higher resolution may be required for scanned graphics. When saving scanned documents, lossy compression should only be used with caution as it might compromise legibility. For example, visible artifacts may be created around complex high-contrast image areas like text. Therefore such images are unsuitable for lossy compression, as opposed to continuous-tone photographic images.
Source format	PDF files should be created (rendered) directly from their electronic source documents, except where the applicant has no access to the electronic source document.

In addition, care should be taken in the settings defined for the PDF writer used to ensure that no device-specific options are embedded in the PDF file (i.e. for a specific physical output device like a printer) as the file format should be device-independent.

3 Other File Formats

The default file format for narrative documents that need no subsequent editing is PDF. For graphic documents the use of PDF is also recommended. When appropriate, also the following file formats may be used:

- Joint Photographic Experts Group (JPEG),
- Scalable Vector Graphics (SVG),
- Graphics Interchange Format (GIF) and
- Tagged Image File Format (TIFF) [ISO 12234-2:2001].

4 References

[IEC 61966-2-1:1999] Multimedia systems and equipment – Colour measurement and management – Part 2-1: Colour management – Default RGB colour space – sRGB.

[ISO 12234-2:2001] Electronic still-picture imaging -- Removable memory -- Part 2: TIFF/EP image data format.

[ISO-19005-1:2005] Document management -- Electronic document file format for long-term preservation -- Part 1: Use of PDF 1.4 (PDF/A-1).

[ISO-19005-2:2011] Document management -- Electronic document file format for long-term preservation -- Part 2: Use of ISO 32000-1 (PDF/A-2).

[ISO 19005-3:2012] Document management -- Electronic document file format for long-term preservation -- Part 3: Use of ISO 32000-1 with support for embedded files (PDF/A-3).

[ISO 32000-1:2008] Document management -- Portable document format -- Part 1: PDF 1.7.[1]

[1] An ISO approved copy of the ISO 32000-1 standards document is available as a free PDF on the Adobe Web site (http://www.images.adobe.com/www.adobe.com/content/dam/Adobe/en/devnet/pdf/pdfs/PDF32000_2008.pdf). It is not an official ISO document but the technical content is identical and page and section numbers are preserved.